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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/518,177	12/15/2004	David Bonnaffe	10404.004.00-US	5723

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EXAMINER	
KRISHNAN, GANAPATHY	

ART UNIT	PAPER NUMBER
1623	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/518,177	BONNAFFE ET AL.	
	Examiner	Art Unit	
	Ganapathy Krishnan	1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 December 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-43* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-43* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *15 December 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *03/04/2005*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claim Objections

Claims 24-28, 36-37 and 41 are objected to because of the following informalities: Claims 24-28 are drawn to compounds of claim 1 and further recite intended use and are therefore seen as duplicates of claim 1. Claims 36-37 and 41 are duplicates of claim 35. The said claims either have to be cancelled or rewritten to further limit the parent claim from which they depend. Appropriate correction is required.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 25, 32-34 and 42-43 are rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd.* v. *Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 27-28, 32-34, 38-40 and 43 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the compound of formula (I) and the process of making it, does not reasonably provide enablement for the use of the said compounds in the treatment of the diseases and prevention of transplant rejection as recited in the instant claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

A conclusion of lack of enablement means that, based on the evidence regarding each of the factors below, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation.

(A) The breadth of the claims
(B) The state of the prior art
(D) The level of predictability in the art
(D) The amount of direction provided by the inventor
(E) The existence of working examples
(F) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

The breadth of the claims

The instant claims are drawn to the use of the compounds of formula (I) for the treatment of autoimmune, inflammatory, degenerative diseases and preventing transplant rejection. The terms, autoimmune, inflammatory, degenerative diseases recited in the claims are broad recitations and are seen to include several disorders and conditions of which only a few are recited in the instant claims as examples. These broad recitations are also seen to include diseases/disorders and conditions that are unknown as of the filing date of the instant application.

The state of the prior art

The examiner notes that the art cited by the applicants and used in the rejection below, teaches the use of carbohydrates for modulating the activity of γ-interferon. However, there is no teaching of the treatment or prevention of diseases and conditions in the prior art. One of ordinary skill in the art would not extrapolate the information in the prior art to the treatment of all of the said diseases and conditions encompassed by the broad recitations in the instant claims.

The level of predictability in the art

There is not seen sufficient data to substantiate the treatment of the said diseases and conditions or prevention of transplant rejection using the compounds of this invention. Autoimmune diseases are characterized by the body's immune responses being directed against its own tissues, causing prolonged inflammation and subsequent tissue destruction. Autoimmune disorders can cause immune-responsive cells to attack the linings of the joints--resulting in rheumatoid arthritis--or trigger immune cells to attack the insulin-producing islet cells of the pancreas leading to insulin-dependent diabetes. A healthy immune system recognizes, identifies, remembers, attacks, and destroys bacteria, viruses, fungi, parasites, and cancer cells or any health-damaging agents not normally present in the body. A defective immune system, on the other hand, wreaks havoc throughout the host by directing antibodies against its own tissues. Any disease in which cytotoxic cells are directed against self-antigens in the body's tissues is considered autoimmune in nature. Such diseases include, but are not limited to, celiac disease, Crohn's disease, pancreatitis, systemic lupus erythematosus, Sjogren's syndrome, Hashimoto's thyroiditis, and other endocrinopathies. Allergies and multiple sclerosis are also the result of disordered immune functioning. The diseases and conditions encompassed by the instant claims

all have different etiologies and the said treatment using the compounds of the instant invention of all the diseases/conditions is highly unpredictable.

The amount of direction provided by the inventor

The instant specification is not seen to provide enough guidance that would allow a skilled artisan to extrapolate from the disclosure the treatment and prevention methods o all the disease/conditions as instantly claimed. The specification also fails to direct the skilled artisan in correlative prior art procedures which might provide the basis for the said treatment. Applicants state that (specification, page 18, last paragraph) that pro-inflammatory cytokines like IFN-γ are associated with several diseases. This does not mean that modulating IFN-γ alone would treat the disease/conditions as instantly claimed or prevent transplant rejection.

The existence of working examples

The working examples set forth in the instant specification are drawn to the synthesis of compounds of formula (I). There is no enabling disclosure/examples for the treatment of the disease/conditions as instantly claimed.

The quantity of experimentation needed to make or use the invention based on the content of the disclosure

Indeed, in view of the information set forth, the instant disclosure is not seen to be sufficient to enable the use of the instant compounds for the treatment of the diseases/conditions and prevention of transplant rejection as instantly claimed. One of ordinary skill in the art would have to carry out experimentation in order to determine the efficacy of the said compounds in the said methods of treatment.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-43 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Regarding claim 1, the phrase "for example" renders the claim indefinite because it is unclear whether the limitation(s) following the phrase are part of the claimed invention. See MPEP § 2173.05(d). The said recitation is also seen in claims 8, 18, 26, 28, 30, 31, 33, 39, 40 and 43.

Claims 3 and 6 recite the term preferably. It is not clear if applicants intend only the range following the said recitation or a range outside the preferred range or another similar agent is also acceptable.

Regarding claim 6, the phrase "such as" renders the claim indefinite because it is unclear whether the limitations following the phrase are part of the claimed invention. See MPEP § 2173.05(d). The said recitation is also seen in claims 27, 30 and 33.

Claim 18 recites, "coupling of two water soluble compounds that are precursors of formula (III)" and "a dithiol compound that is a precursor of the spacer groups ". The claim recitation is not clear. The claim is drawn to preparing the compound of formula (II), which is seen to have the structures recited in claim 18. But the claim recites coupling of compounds that are precursors of the recited formula in claim 18. If the precursors of formula (III) and the dithiol are used in the coupling, what are they? It looks like the compound of formula (III) is coupled to the dithiol but the claim language is confusing. The claim further recites that the coupling is

carried to obtain compound of formula (IV) but the claim does not recite the structural formula for compound (IV). The claim also does not end with a period. This renders the claim indefinite since it is not clear if the claim ends as recited or if additional text is intended after formula (II).

Claims 25, 32-34 and 42-43 provide for the use of the compounds pf claim 1, but, since the claim does not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

The term "excessive" in claim 32 is a relative term which renders the claim indefinite. The term "excessive" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

Claims that depend from a rejected base claim that is unclear/indefinite are also rendered unclear/indefinite and are rejected for the same reasons.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-17 and 24-43 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lorat-Jacob (WO 97/03700, English Translation; Dcoument B1 in IDS of 03/04/2005) in view of Morel et al (Cytokine, 1996, 8(7), 557-566; Document C2 in IDS of 03/04/2005) and Turnbull et al (WO 93/19096).

Lorat-Jacob, drawn to γ-interferon, teaches agents for the modulation of γ-interferon activity. The agents are of the type A-X-B, wherein A and B are oligosaccharide groups that carry anionic charge to confer affinity for the C-terminal portion of γ-interferon containing the peptide sequence 125-131, and X is a spacer arm connecting A and B via covalent bonds (page 6, lines 5-16). The modulating agent consists of oligosaccharide groups sulfate and/or phosphate groups. The oligosaccharide units A and B contain units that are derived from an N-sulfated osamine or units derived from sulfated uronic acids, notably containing alternating disaccharide units derived from uronic acid as in glycosaminoglycans. The fragments A and B are those

preferably obtained from heparan sulfate and can be 6-14 saccharide units long. The spacer X can be any polymer for example polyoside or polyglycol having sufficient length to allow the units A and B to bind to the C-terminal ends of γ-interferon. The polyglycol unit can be a poly(alkylenoxy)arm (page 8). The length of the spacer X can be determined by routine experimentation. In specific embodiments the spacer arm can contain anionic groups like sulfate, phosphate or carboxylic groups and one can also use natural polyosides cellulose, starch, glycosaminoglycans (page 9, lines 1-15). The units A and B can also be fragments obtained from heparin (page 11, lines 1-7).

According to Lorat-Jacob, the agent of his invention can be used as a drug (medicament) to modulate the activity of γ-interferon. It can also be used in combination with γ-interferon (medicament or complex as instantly claimed) comprising vehicles and adjuvants, as a lyophilizate or in the form of an aqueous solution (pages 12-13). However, Lorat-Jacob et al do not exemplify a compound of instant formula (I), wherein the spacer group X is a group as recited in instant claims 7-17 and wherein the saccharide units on either side of the spacer group are symmetrical. But there is a suggestion of compounds of instant formula (I) comprising saccharide units as in formula (I) and substitutions and spacer groups and their length as recited in instant claims 1-6.

Morel et al, drawn to γ-interferon and the role of heparan sulfate, teach that the concept that cytokine and growth factor activity is governed not only by their bindings to specific cell surface receptors, but also to extracellular components is well accepted and that the interaction of γ-interferon with heparan sulfate/heparin-like molecules result in a tight control of the cytokines (page 564, right column, first full paragraph). This teaching of Morel and the teaching of Lorat-

Jacob as explained above, suggests to one of ordinary skill in the art that saccharide oligomers that have heparin or heparan sulfate monomeric units comprising glucosamine units and glucuronic acid units are important for binding to cytokines like γ-interferon in order to modulate their activity.

Turnbull et al, drawn to oligosaccharides, teaches that heparin or heparan sulfate with the complexity and heterogeneity with a large number of different disaccharide units may have different activities and have undesirable side effects and would lack specificity in binding to growth factors on cell surfaces. What is needed is a substantially homogenous preparation of a relatively small molecular compound (page 4, line 38 through page 5, line 13). This means that the structure of the saccharide units in heparin or heparan sulfate should be same or uniform for reducing the side effects and increasing the beneficial activity, i.e., binding to cytokines like γ-interferon by heparin and heparan sulfate fragments that are extracellular components (as taught by Morel above). Hence this is a suggestion to make fragments A and B in the compounds of Lorat-Jacob uniform or symmetrical so that the binding to γ-interferon is the main reaction that takes place and not any other side reaction that is not beneficial. Lorat-Jacob also suggests that in their compound A-X-B, the fragments A and B may be similar (Lorat-Jacob, page 7, lines last three lines).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to make compounds of instant formula (I) and their compositions and complexes with γ-interferon as a medicament for modulating the activity of γ-interferon and thereby treatment of cancers and infectious diseases of viral, bacterial or parasitic origin (Lorat-Jacob page 13, first

full paragraph) since such is seen to be taught in the prior art using closely analogous compounds.

One of skill in the art will be motivated to make and use the compounds in the methods of treatment of diseases associated with cytokines like γ-interferon since such compounds having a uniform structure in the carbohydrate fragments is taught in the prior art to have reduced side effects and side reactions and hence would bind only to γ-interferon, thereby achieving better modulation of the γ-interferon activity. This would enhance the beneficial effects of the compounds as instantly claimed.

Conclusion

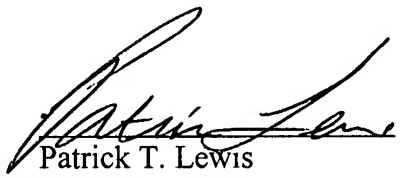
Claims 1-43 are rejected

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ganapathy Krishnan whose telephone number is 571-272-0654. The examiner can normally be reached on 8.30am-5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shaojia A. Jiang can be reached on 571-272-0627. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

GK



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